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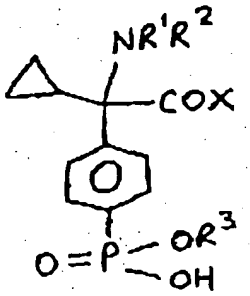
(54) Title: ALPHA-CYCLOPROPYL-SUBSTITUTED PHENYLGLYCINES AS CNS AGENTS

(57) Abstract

Compounds of formula (I) are provided wherein: R^1 and R^2 are independently selected from hydrogen, optionally substituted alkyl and optionally substituted acyl; R^3 is hydrogen or an optionally substituted group selected from alkyl, aryl and aralkyl; and X is OR^6, where R^6 is hydrogen or optionally substituted alkyl, or NR^4R^5, where R^4 and R^5 are independently selected from hydrogen and optionally substituted alkyl, optionally substituted on the phenyl ring. The compounds have activity at receptor sites in the central nervous system.



(I)

ALPHA-CYCLOPROPYL-SUBSTITUTED PHENYLGLYCINES AS CNS AGENTS

This invention relates to compounds having activity at receptor sites in the central nervous system (CNS). In particular, the invention relates to phenylglycine derivatives which have a cyclopropyl group at the α-position and to pharmaceutical compositions comprising these compounds.

Various amino acids have recently become of interest following the discovery that they are able to influence the activity of certain receptor sites in the CNS and attention has been directed to the identification of material that will have specific action in relation to these receptor sites with a view to identifying compounds that can be used to control various disorders resulting from central nervous malfunction such as involuntary muscular activity and mental, affective or memory disorders. The compounds might also be used to control the perception of the sensation of pain.

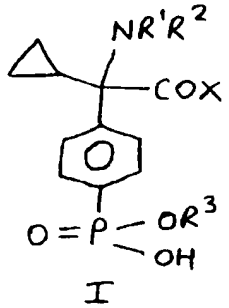
It is known that certain aryl compounds derived from 2-amino-2-phenylacetic acid (phenylglycine) bearing hydroxy and/or carboxy substitutents in the phenyl ring and an alkyl or substituted alkyl or aryl substituent in the 2-position of the acetic acid moiety have actions at certain amino acid receptor sites in the CNS which are involved in the control of the transmission of nerve impulses in the brain and spinal cord, including those underlying memory processes and the perception of pain.

Compounds having activity at receptor sites in the CNS are disclosed WO 95/15941. This document discloses a large group of aryl substituted amino acids but specific mention is made of only one compound containing a cyclopropyl group i.e., 2-cyclopropyl-2-(4-carboxyphenyl) glycine. The compounds are described as having activity at metabotropic glutamate receptors (mGluRs).

To date molecular biologists have discovered eight sub-types of metabotropic glutamate receptor (mGluR) which have been divided into three main sub groups according to their sequence homology, signal transduction mechanism and their agonist selectivity. Sub group I mGluRs consist of mGluR 1 and 5 and are selectively activated by (1S, 3R)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD). Sub group II mGluRs consist of mGluR 2 and 3 and are selectively activated by (1S, 3S)-ACPD. Sub group III mGluRs consist of mGluRs 4, 6, 7 and 8 and are potently activated by L-2-amino-4-phosphonobutanoate (L-AP4).

It has now been found that a group of α-cyclopropyl substituted phenylglycine compounds has unexpectedly improved pharmacological properties over those previously disclosed, for example, in WO 95/15941. These advantages include greatly enhanced potency in their activity at mGluRs and higher selectivity for this type of receptor. The compounds are also selective for certain groups of mGluR. Specifically, the compounds act as potent and selective sub group III mGluR antagonists.

Accordingly, the present invention provides compounds of formula I



I

wherein: R^1 and R^2 are independently selected from hydrogen, optionally substituted alkyl and optionally substituted acyl;

R^3 is hydrogen or an optionally substituted group selected from alkyl, aryl and aralkyl; and

X is OR^6, where R^6 is hydrogen or optionally substituted alkyl, or NR^4R^5, where R^4 and R^5 are independently selected from hydrogen and optionally substituted alkyl,

optionally substituted on the phenyl ring

and pharmaceutically acceptable salts thereof.

The term "alkyl", as used herein, covers both straight chain and branched alkyl groups which have from 1 to 6 carbon atoms such as methyl, ethyl, propyl and butyl . An analagous convention applies to the term "acyl".

The alkyl and acyl groups in the compounds of the invention are optionally substituted by one or more groups selected from halogen, hydroxy, amino, carboxy, oxo, phosphono, $-PO_2H(OR^7)$, phosphinico, $-PO_2H(R^7)$, $-OPO_3H_2$, $-OPO_2H(OR^7)$, arsono, $-AsO_2H(OR^7)$, arsinico, $-AsO_2H(R^7)$, tetrazolyl, sulpho, sulphino, sulpheno, nitro, cyano, thio, $-OSO_3H$, aryl, and further optionally substituted alkyl or acyl groups. R^7 is hydrogen or alkyl.

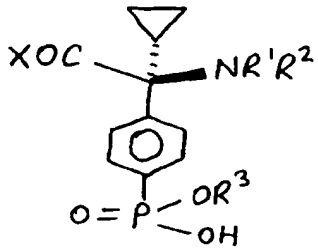
The term "aryl", as used herein, includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from halogen, nitro, cyano, alkyl, acyl, hydroxy, carboxy, amino, phenyl, alkylcarbonyloxy, alkoxycarbonyl, formyl or alkylcarbonyl. The term "aralkyl" refers to an alkyl group substituted with an aryl group such as optionally substituted benzyl.

The phenyl ring in the compounds of the invention may be substituted by from one to four groups selected from halogen, hydroxy, amino,carboxy, phosphono, $-PO_2H(OR^7)$, phosphinico, $-PO_2H(R^7)$, $-OPO_3H_2$, $-OPO_2H(OR^7)$, arsono, $-AsO_2H(OR^7)$, arsinico, $-AsO_2H(R^7)$, tetrazolyl, sulpho, sulphino, sulpheno, nitro, cyano, thio, $-OSO_3H$ and optionally substituted alkyl, acyl or aryl. Substitution by halogen (especially chlorine) is preferred, particularly at the 3-position of the aromatic ring.

When used herein, the term "halogen" refers to fluorine, chlorine, bromine or iodine and an analagous convention applies to the term "halide".

The compounds of the invention have an asymmetric carbon atom bound to the phenyl ring and the invention includes racemic mixtures and

the individual stereoisomers. Preferably, the compound of formula I has the following stereochemistry at the carbon atom bound to the phenyl ring:



These enantiomers, conventionally designated as having S configuration, have been found to be particularly selective in their activity at mGluRs.

So far as the compounds of the invention contain other asymmetric centres, by virtue of optional substituents, the invention covers both optically active forms and racemic mixtures.

The compounds may take the form of the free compound as indicated in formula I or they may be in the form of their pharmaceutically acceptable salts. For example, the salts may be physiologically acceptable acid addition salts of a basic amino group in the molecule such as salts with hydrochloric acid, acetic acid, succinic acid, tartaric acid or citric acid. Salts may also be formed with an acidic group in the molecule, such as a carboxy or phosphono group, and suitable examples of this type of salt are mono-, di- and poly- sodium salts. When the compounds of the invention contain both basic and acidic groups, either or both of the basic and acidic groups can be present as salts.

The present invention includes compounds which are hydrolysable in vivo to compounds of formula I, such as the esters or amides of optional substituents.

Formula (I) includes solvates of the compound, such as with solvents used for purification of the compound e.g., by crystallisation.

Preferably R^1 and R^2 are both hydrogen. Suitably, X is OH. R^3 is conveniently hydrogen.

A particularly preferred compound of the invention is 2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid and its pharmaceutically acceptable salts. Also preferred is 2-amino-2-cyclopropyl-2-(3-chloro-4-phosphonophenyl)acetic acid and its pharmaceutically acceptable salts.

The present invention also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable diluent or carrier. The use of the compounds for the treatment of a disorder of the CNS which comprises the administration to a patient of a pharmacologically effective amount of a compound or the composition of the invention is also contemplated, as is the use of the compounds in the manufacture of a medicament for the treatment of disorders of the CNS.

As a result of their activity as selective antagonists at mGluRs, the compounds of the invention depress nociceptive responses and may be used as analgesics. They may also be used in the treatment of other disorders of the CNS by utilisation of their selective antagonist activity at mGluRs, particularly sub group III mGluRs.

The compounds and compositions of the invention may be administered parenterally or orally, for example, intravenously for acute treatment or subcutaneously or orally for chronic treatment. The compounds may be formulated for clinical use in suitable vehicles, normally as a preparation of a water-soluble salt, though preparations of low water solubility, possibly in association with physiologically tolerable emulsifying agents, may be used for depot administration.

Since it is believed to be necessary for compounds of the invention to penetrate the blood brain barrier, it is frequently necessary to administer the compounds of the present invention in amounts significantly in excess of the amounts necessary to be achieved within the brain for the therapeutic effect desired and this will influence the concentration of the active

compounds in the composition of the present invention. Considerations of this type suggest that such a conventional dosage volume would provide the subject with up to about 200 mg/kg body weight although, when the compounds are to be administered by the intravenous route, dosages in the region of about 1-20 mg/kg body weight are to be expected for the more active compounds and/or for those substances with a high lipophilic or hydrophilic balance.

The compounds of the invention are also useful as research tools for investigating mechanisms of CNS activity. Thus, they may be used as radioactive ligands for receptor binding and metabolic studies. Formula I therefore includes radiolabelled compounds. Suitable radiolabelling includes, for example, the incorporation of an atom of a radioisotope such as tritium or iodine-125 into the compounds.

The compounds of the invention will also be useful for the isolation of receptors from central nervous tissue by, for example, linking the molecules via a spacer molecular chain to an affinity chromatography support material of the sepharose or agarose type.

The compounds of the invention may be prepared by methods well-known in the art, particularly by employing known methods of amino acid synthesis. Suitable synthetic methods are disclosed in WO 95/15941, for example, and include reactions involving the Strecker synthesis and the Bucherer-Berg synthesis. Hence, the compounds can be prepared by the reaction of the corresponding phenyl cyclopropyl ketone with an ammonium salt and a cyanide salt (e.g., ammonium carbonate, ammonium chloride and potassium cyanide) to convert the ketone group into an amino acid, followed, if necessary, by forming or adding the desired phosphono substituent at the 4- position on the phenyl ring.

Compounds of formula I which are substantially one optical isomer or are enriched in a particular optical isomer may be prepared by known stereoselective synthetic methods such as the established routes for

preparing amino acids using chiral reagents. Alternatively, optically active samples of the compounds can be prepared from the corresponding racemic mixtures by classical resolution procedures e.g., fractional crystallisation of the salt formed with R or S lysine or arginine, as appropriate.

The compounds may be purified using known chromatography techniques and/or by recrystallisation from a suitable solvent or mixture of solvents.

EXAMPLES

EXAMPLE 1

(RS)-2-Amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid

(i) Synthesis

To a stirred mixture of 4-chlorophenyl cyclopropyl ketone (10g, 55.4 mmol) was added triethyl phosphite (2 ml) and anhydrous nickel chloride (0.73g) at 180-210°C for 3h. The mixture was cooled to room temperature and poured into water (100 ml). The resulting mixture was extracted with ethyl acetate (3 x 150 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The yield of crude cyclopropyl 4-(diethoxyphosphinyl)phenyl ketone was essentially quantitative.

Crude cyclopropyl 4-(diethoxyphosphinyl) phenyl ketone (15.6g, 55.4 mmol), ammonium carbonate (53.2g, 554 mmol), ammonium chloride (5.9g, 110 mmol) and potassium cyanide (18g, 277 mmol) in methanol (50 ml) and water (50 ml) were stirred at 65°C for 72h.

The mixture was then boiled in an open flask to eliminate excess ammonium carbonate. Concentrated HCl (100 ml) was carefully added and

the resulting mixture heated under reflux for 24h. Next day, the solution was evaporated under reduced pressure, the residue dissolved in a minimum amount of water and applied to a bed of AG50 H^+ ion-exchange resin. The column was eluted with water and then 1.0 M aqueous pyridine. The ninhydrin positive fractions of the 1.0 M aqueous pyridine eluate were combined and evaporated. The residue was dissolved in a minimum amount of water and applied to a bed of Dowex AG1 acetate ion-exchange resin. The column was eluted with water and then a gradient of aqueous acetic acid. Ninhydrin-positive fractions of the aqueous acetic acid eluate containing the desired compound were combined and evaporated. The residue was crystallized from ethanol/water. It gave (RS)-2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid, (540 mg) as a white solid.

270 MHz ^1H nmr (D_2O/NaOD, standard $Me_3Si(CH_2)_3SO_3Na$): δ 0.3-0.74 (m, 4H), 1.57 (m, 1H), 7.51 (m, 2H), 7.65 (m. 2H); 300 MHz ^{13}C nmr (D_2O/NaOD, standard $Me_3Si(CH_2)_3SO_3Na$): δ 2.65, 3.78, 20.73, 66.65, 128.25, 128.41, 132.68, 132.79, 142.98, 148.88, 185.29.

For $C_{11}H_{14}NO_5P.0.25H_2O$

Calculated C, 47.92; H, 5.30; N, 5.08%

Found C, 47.70; H, 5.61; N, 4.84%

(ii) Pharmacological Data

Table 1 shows antagonism by α-substituted-phenylglycines of L-AP4- and (1S, 3S)-ACPD- induced depression of dorsal root-evoked monosynaptic excitation of neonatal rat motoneurones.

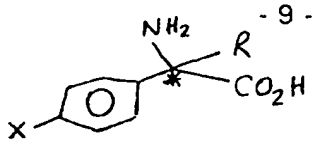


Table 1

Compound	R	X	Stereochemistry (*)	Apparent KD (μM) versus L-AP4	Apparent KD (μM) versus (1S,3S)-ACPD
CPPG		PO_3H_2	RS	2.5 ± 0.3	51 ± 3
MCPG[1]	Me	CO_2H	S	227 ± 12	9 ± 37
MPPG[2]	Me	PO_3H_2	RS	9.2 ± 0.3	113 ± 13
MTPG[2]	Me	Tetrazole	RS	188 ± 9	77.2 ± 7

[1] Values taken from Kemp et al (1994) Eur.J.Pharmacol-Molec.Pharmacol.Sect. 266 187-192

[2] Values taken from Jane et al (1995) Neuropharmacology 34 851-856

The pharmacological data show the enhanced potency of the compound and the greater selectivity for sub group III mGluRs over sub group II mGluRs. The compound is over three times as potent and more selective by a factor of about two, than the closely related α-methyl substituted compound. In one aspect, therefore, the invention can be seen to be based on the selection of 2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid and analagous compounds from the broad disclosure in the prior art.

Table 2

Compound	IC_{50} (nM) for reversal of inhibition of forskolin-stimulated cyclic AMP accumulation in adult rat cortical slices mediated by: L-AP4 (10 μm)	L-CCG-I (300 nM)
MPPG[3]	156 ± 29	69.5 ± 0.5
CPPG[4]	2.2 ± 0.6	46.2 ± 18.2

[3] Taken from Bedingfield et al., Eur, J. Pharmacol., 1996, 309, 71-78

[4] Taken from Toms et al., Br. J. Pharmacol., 1996, 119, 851-854

Table 2 shows antagonism by (RS)-MPPG and (RS)-CPPG of L-AP4- and L-CCG-I- induced inhibition of forskolin stimulated cyclic AMP accumulation in adult rat cortical slices. This data also shows the enhanced potency and greater selectivity of CPPG over previously reported compounds for subgroup III mGluRs (activated by L-AP4) over subgroup II mGluRs (activated by L-CCG-I). In this analysis, CPPG is more than 70 times more potent and also more selective for subgroup III mGluRs than the closely related α-methyl compound.

EXAMPLE 2

(RS)-2-Amino-2-cyclopropyl-2-(3-chloro-4-phosphonophenyl) acetic acid

A mixture of cyclopropyl (3-chloro-4-diethoxyphosphinylphenyl) ketone (7.86 g 24.8 mmol), potassium cyanide (8.06 g, 124 mmol), ammonium carbonate (23.8 g, 248 mmol) and ammonium chloride (2.65 g, 49.6 mmol) in 50% ethanol (200 ml) was heated to 60°C overnight. Next day, the mixture was cooled and evaporated and 6N aqueous hydrochloric acid (400 ml) was added to the residue. The mixture was heated under reflux overnight. Next day, the mixture was cooled, extracted with ethyl acetate (3 x 200 ml) and the aqueous layer evaporated under reduced pressure. The residue was dissolved in water and applied to a Dowex 50WX8-400^R (H^+ form) ion-exchange resin column (1L). The column was eluted with water until the eluate had a pH of about 5 and then elution was continued with 2M aqueous ammonia. Ninhydrin positive fractions of the aqueous ammonia eluate were combined and evaporated. The residue was dissolved in water and applied to a Dowex 1X8-400^R (acetate form) ion-exchange resin column (100 ml). The column was eluted with water and

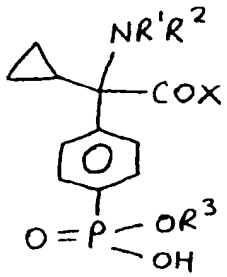
then successively with 0.1N, 0.5N, 1.0N, 2.0N, 3.0N and 4.0N aqueous acetic acid (500 ml of each). Ninhydrin positive fractions of the 4.0N aqueous acetic acid eluate were combined and evaporated. The resulting solid was crystallised from ethanol/water to give the title compound (130 mg) as a white solid.

300 MHz ^{1}H nmr (D_2O, NaOD, $Me_3Si(CH_2)_3SO_3Na$ as standard): δ 7.94 (1H, m), 7.77 (1H, m), 7.55 (1H, m), 1.65 (1H, m), 0.75 (3H, m) and 0.5 (1H, m).

Paper electrophoresis (pH4 buffer, 4 Kv): mobility relative to glutamic acid = 1.4. R_f = 0.5 (Silica gel coated tlc plates, eluent: (pyridine (3):acetic acid (8):water (11)): n-butanol 3:2)

CLAIMS

1.Compound of formula I



I

wherein: R^1 and R^2 are independently selected from hydrogen, optionally substituted alkyl and optionally substituted acyl;

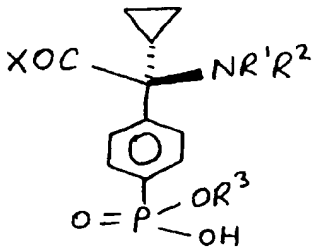
R^3 is hydrogen or an optionally substituted group selected from alkyl, aryl and aralkyl; and

X is OR^6, where R^6 is hydrogen or optionally substituted alkyl, or NR^4R^5, where R^4 and R^5 are independently selected from hydrogen and optionally substituted alkyl,

optionally substituted on the phenyl ring

and pharmaceutically acceptable salts thereof.

2.Compound as claimed in claim 1 which has the following stereochemistry



3. Compound as claimed in claim 1 or claim 2, wherein R^1 and R^2 are both hydrogen.

4.Compound as claimed in any one of claims 1 to 3, wherein X is OH.

5.Compound as claimed in any one of claims 1 to 4, wherein R^3 is hydrogen.

6. Compound as claimed in any one of claims 1 to 5, wherein the phenyl ring has a chlorine atom substituted at the 3-position.

7.Compound as claimed in claim 1 which is 2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid or a pharmaceutically acceptable salt thereof.

8. Compound as claimed in claim 1 which is 2-amino-2-cyclopropyl-2-(3-chloro-4-phosphonophenyl) acetic acid or a pharmaceutically acceptable salt thereof.

9.Pharmaceutical composition comprising a compound of any one of claims 1 to 8 together with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

Inte· 'ional Application No
PC·/GB 96/03073

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BR. J. PHARMACOL. (BJPCBM,00071188);96; VOL.119 (5); PP.851-854, - 21 October 1996 UNIVERSITY OF BRISTOL;DEPARTMENT OF PHARMACOLOGY; BRISTOL; BS8 1TD; UK (GB), XP000618728 TOMS N J ET AL: "The effects of (RS)-.alpha.-cyclopropyl-4-phosphonophenyl glycine ((RS)-CPPG), a potent and selective metabotropic glutamate receptor antagonist" see the whole document ---	1-9

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inv· ·tional Application No
Pc·/GB 96/03073

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9515941 A	15-06-95	AU 1246895 A	27-06-95
		EP 0733037 A	25-09-96
EP 318935 A	07-06-89	US 5175153 A	29-12-92
		AT 118009 T	15-02-95
		DE 3852935 D	16-03-95
		DE 3852935 T	24-05-95
		ES 2068194 T	16-04-95
		JP 1230590 A	14-09-89